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MOUTH DISSOLVING FILMS: AN INNOVATIVE DRUG DELIVERY SYSTEM

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ABSTRACT

Now a days new techniques are developing in every sector, many of the pharmaceutical groups are focusing their research on mouth dissolving technology. Mouth Dissolving Films technology is gaining much attention. Dosage forms like tablets, syrup and injections are expensive and time consuming, so developing the innovative drug delivery for the existing drug have been done. Mouth dissolving film is the Novel drug delivery system consisting of a very thin oral strip which gives onset of action, without drinking water or swallowing. Mouth Dissolving Films evolved over the past few years from the confection and oral care markets in the form of breath strips and has become a novel delivery system. Hence it gives site specification and local action and leads to better bioavailability of drug. The formulation is convenient for pediatrics, geriatrics and bedridden patients. This review describes about the formulation methodology, evaluation parameters and the future aspects of mouth dissolving films.

KEYWORDS: Mouth Dissolving Films, oral strip, rapid disintegrating, novel delivery system.

INTRODUCTION

Oral route of administration is the most convenient and preferred route of administration among the various other delivery system. More than 70% of drugs are available in the market in the form of oral drug delivery system due for pain avoidance and versatility (to accommodate various types of drug candidates). Mouth dissolving films (MDFs) is one of the simplest preparations.[11] It is an ultrathin strip of postage stamp size with an active agent and other excipients developed on the basis of transdermal patch technology. MDFs by solvent casting method is the simple and cheapest method of preparation. Whereas the other dosage forms like tablets require various granulation process, punching, and coating. Liquid preparations such as syrup should maintain the stability of the product to overcome disadvantages associated with above solid and liquid preparations Mouth Dissolving Films (MDFs) were developed.[22] Mouth dissolving dosage form has become increasingly important because of their unique properties. They quickly disintegrate and dissolve, and can be administered without water, making them particularly suitable for pediatrics and geriatric patients. Mouth dissolving films (MDFs), have gained popularity not only in breath strips but also in personal care, food and drug.[1]

Now a days MDFs are well proven and accepted technology for the systemic delivery of active pharmaceutical ingredients. MDFs can be used for various category of drugs Such as antiulcer, antiasthmatic, antiepileptic, hypertension, heart attack, motion sickness, antitussive, paralysis, mental disorders, and repeated emesis.[2]

Advantages of mouth dissolving films over other dosage form

The poorly soluble drugs can be incorporated into the MDFs. MDFs rapid production is possible since the process involves only two steps, mixing followed by casting. Mouth dissolving films are patient friendly, MDF have a much larger surface area than the other delivery methods. MDFs are available in different pleasant flavors and colors. It is a kind of precision medication with perforations in single films that offers dosing accuracy and flexibility. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in the side effects associated with molecules. It requires less energy consumption in preparation compared with high shear methods as in liquid formulations. It involves fewer processing steps. Compressibility properties of the API may not be of importance. It gives good dispersion mechanism for poorly soluble drugs. More uniform dispersion of the fine particles because of intense mixing and agitation. Easy for administration to the pediatric, geriatric and bedridden patients who find difficulty to swallow tablets and hard gelatin capsules. No need of water to swallow the dosage form which helps for the patients who are travelling. The risk of chocking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety. It is very useful in cases where a rapid onset of

action is required such as in sudden episodes of allergic attack, motion sickness, bronchitis or asthma. Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So it gives advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability. It offers other advantages such as improved portability, accurate dosing, Cost effectiveness and improved patient complains.[13]

Pharmaceutical companies and customers practically accepted MDFs as an alternative of conventional OTC dosage forms such as tablets and capsules etc. From commercial point of view, MDFs provide new business opportunity like product differentiation and promotion. MDFs are loaded with sensitive reagent to allow controlled release when exposed to biological fluids or to create isolation barriers for separating multiple reagents to enable a timed reaction with a diagnostic device. Flexible and portable nature allows ease in transportation, storage and handling.[6]

Disadvantages

Dose uniformity is a technical challenge. High doses cannot be incorporated (<40mg/4cm²). It requires special package for products stability and safety. It has hygroscopic nature thus must be stored in dry place. Some time it shows the fragile and granular property. Some drugs are unstable at buccal pH cannot be administered.[7,17]

Table 1: Comparison between mouth dissolving film and oral tablets.

Sl. No.	Mouth dissolving films	Oral tablets
1	Mouth dissolving films have greater dissolution due to large surface area	Oral Tablets have lesser dissolution due to lesser area compare to oral films
2	They have better longevity than Oral tablets	They have less longevity than oral films
3	They have more patient compliance than oral tablets	They have less patient compliance as compare to oral film
4	There is no risk of choking	There can be risk of choking.[27]

Classification of Mouth Dissolving Films

There are three different subtype of mouth dissolving film

1. Mucoadhesive sustained release wafer
2. Mucoadhesive melt away wafer
3. Flash release wafer.[27]

1. Mouth adhesive sustained release wafer

- It is applied to the gingival or oral cavity
- Drugs are dispersed in solid solution or suspension.
- Non soluble polymers are used.
- Excipients with low solubility are used
- Multi layered structure
- Area 2-4 cm^2
- Thickness 50-250mm
- Dissolution 8-10h

2. Mucoadhesive melt away wafer

- It is applied to the gingival or buccal region.
- Drugs dispersed in solid solution or suspension
- Hydrophilic polymers are required
- Soluble excipients are used
- single or multilayered structure
- area 2-7 cm^2
- thickness 50-500mm
- dissolution 1-3min

3. Flash release wafer

- It is applied to the upper plate of the tongue
- Drugs are dispersed in solid solution phase
- Highly hydrophilic polymer used
- Soluble excipients are used
- Single layered structure
- Area 2-8cm^2
- Thickness 20-70mm
- Dissolution within 60s maximum.

Mechanism of Action

Anatomy and physiology of oral cavity

The various target sites for drug delivery may include- The inner surfaces of the upper and lower lips, gums (gingiva), hard and soft palate, floor of the mouth (sublingual), tongue and buccal mucosal tissue (cheek). A drug can be administered via many different routes to produce a systemic pharmacologic effect. In this route drugs penetrate the mucous membrane by simple diffusion and drugs are delivered into the blood stream, which richly nourishes the salivary glands and their ducts and into the systemic circulation via the jugular vein. The majority of drugs move across epithelial membranes, including the oral epithelia, by passive mechanism which is governed primarily by the law of diffusion. In the case of simple diffusion, two potential routes of material transports across the epithelium are-

1. Transcellular pathways
2. Paracellular pathways.

Transcellular route involves transport into and across cells. Paracellular route involves the passages of molecules through intercellular space.

Drug Selection Criteria for Mouth Dissolving Films

- The drug should have pleasant taste.
- The drug to be incorporated should have low dose upto 40mg.
- The drugs with smaller and moderate molecular weight are preferable.
- Good solubility in water as well as in saliva and also

- Should posses good stability.

Formulation Aspects for Mouth Dissolving Films

1) Drug Category
2) Film Forming Polymers
3) Plasticizers
4) Sweetening Agents
5) Saliva Stimulating Agents
6) Cooling Agent
7) Flavoring Agent
8) Coloring Agent
9) Surfactants
10) Stabilizing and thickening agents

Formulation of MDFs involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolution, physical appearance, mouth feel etc. From the regulatory perspectives, all excipients used in the formulation of MDFs should be Generally Regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms. A typical composition is as follows.[18]

1. Drug Category

MDFs technology has the potential for delivery of variety of APIs. However since the size of the dosage form has limitation, high dose drugs are difficult to be incorporated in films. Several classes of drugs can be formulated as mouth dissolving films including antiulcer, antiasthmatics, antitussives, expectorants, antihistaminics and NSAID'S etc.[3,25]

2. Film Forming Polymers

Water-soluble polymers are used as film formers as they provide rapid disintegration, good mouthfeel, and mechanical strength to the films. The robustness of the strip depends on the type of polymer and its amount in the formulations. Water-soluble polymers film, adheres to the buccal mucosa and rapidly delivers medication into the systemic circulation. At least 45%w/w of polymer should generally be present based on the total weight of dry film. Examples of water-soluble polymers include: Pullulan, Gelatin, guargum, Xanthum gum, Hydroxyl propyl methyl cellulose, Modified starches, Hydroxyl ethyl cellulose etc.[5]

3. Plasticizers

Plasticizer is a vital ingredient of the mouth dissolving films. The selection of plasticizer depends upon its compatibility with the polymer and also the type of solvent employed in the casting of film. It helps to improve the flexibility of the film and reduces the brittleness of the film. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. Typically the plasticizers are used in the concentration of 1 - 20%w/w of dry polymer weight. Examples include: Glycerol, Propylene glycol, Low molecular weight polyethylene glycols, Citrate derivatives like triacetin, acetyl citrate, Phthalate derivatives like dimethyl, diethyl, dibutyl derivatives and castor oil etc.[3]

4. Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The sweet taste in formulation is more important in case of pediatric population. Natural sweeteners as well as artificial sweeteners are used to improve the palatability of the mouth dissolving formulations.[17]

Suitable sweeteners include

1. Water soluble natural sweetener: xylose, ribose, glucose, sucrose, maltose, stevioside etc.
2. Water soluble artificial sweetener: sodium or calcium saccharin salts, cyclamate salts, acesulfame-ketc.
3. Dipeptide based sweetener:aspartame

5. Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster dissolution of the film formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.[10,17]

6. Cooling agents

Cooling agents like monomethyl succinate can be added to improve the flavor strength and to enhance the mouth-feel effect of the product. Other cooling agents like WS3, WS23 and Utracoll II can also be used in conjunction with flavors.[21]

7. Flavoring agents

Perception for the flavor changes from individual to individual depending on the ethinicity and liking. It was observed that age plays a significant role in the taste fondness. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers.[21]

8. Coloring agents

Pigments suchas titanium dioxide or FD&C approved coloring agents are incorporated (notexceeding concentration levels of 1%w/w) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form.

9. Surfactants

Surfactants are used as solubilizing or wetting or dispersing agents so that the film gets dissolved within seconds and release active agent immediately. Surfactants also improve the solubility of poorly soluble drugs in mouth dissolving buccal films. Some of the commonly used surfactants are polaxamer 407, sodium lauryl sulfate, benzalkonium chloride, benzthonium

chloride, tweens and spans etc.[15]

10. Stabilizing and thickening agents

The stabilizing and thickening agents are employed to improve the viscosity and consistency of dispersion or solution of the strip preparation solution or suspension before casting. Natural gums like xanthan gum, locust bean gum, carragenan and cellulosic derivatives can be used in the concentration up to 5%w/w as thickening agents and stabilizing agents.[14]

Method of Preparation

1. Casting and drying
a) Solvent casting
b) Semisolid casting
2. Extrusion
a) Hot melt extrusion
b) Solid dispersion extrusion
3. Rolling methods

1. Casting and drying

a) Solvent casting: In this method, first excipients are dissolved in water, then water soluble polymers are added in it finally drug is added and the mixture is stirred to get homogenous solution. The solution is casted in to the petri plate and dried.[13]

b) Semisolid casting: In this method, homogenous viscous solutions are formed by mixing solution of water-soluble film forming polymer and solution of acid insoluble polymer. After Sonication it is coated on non-treated casting film.[19]

2. Extrusion

a) Hot melt extrusion: In this method, the drug is mixed with the carriers in solid form then the extruder having heaters melts the mixture and finally the melt is shaped in to films by the dies.[12]

b) Solid dispersion extrusion: In this method, first drug is dissolved in a suitable liquid solvent and this solution is incorporated in melt of PEG below70^0 C. The selected solvent or drug could not be miscible with melt of PEG and polymorphic form of drug precipitated in solid dispersion may be affected by the solvent.[19]

3 Rolling method: In this method, a solution or suspension containing drug is rolled on acarrier. The ingredients including active agent are dissolved in portion of aqueous solvent using high shear processor. The solvent used is mainly water and mixture of water and alcohol. The film is dried on the rollers and cut in to desired shapes and sizes.[16]

Generally the solvent casting method is employed for manufacture of strips.

Evaluation of Mdfs

1. **Thickness**

The thickness of the film was determined by using a vernier caliper. Film was measured at five different positions i.e. central and four corners and the mean thickness was calculated.[3]

2. **Folding endurance**

Folding endurance was determined repeatedly by folding a small strip of the film at the same place till number of times the film could be folded at the same place without cracking. The studies were performed trice and the mean was calculated.[1]

3. **Drug content**

Drug content was determined by suitable analytical method. Cut the Film into 2×2cm dissolve in 50ml of phosphate buffer pH 6.8 then the solution was filtered through whatman filter paper and diluted if necessary. The resulting solution was measured spectroscopically.[8,24]

4. **Uniformity weight**

Three films were randomly selected and weighed individually then the mean weight and standard deviation of film was calculated.[9]

5. **In vitro disintegration time**

The disintegration time was determined visually in a petri dish containing 20ml of Phosphate buffer pH 6.8 with swirling every 10 seconds. The disintegration time reported was the time when the film starts to break.[2]

6. **Moisture loss**

The moisture loss of the film was determined by placing the known weight and predetermined size of the film in desiccator containing anhydrous calcium chloride for three days. The film were removed and reweight and the percent moisture loss of the film was measured by using the formula.[20]

Percentage moisture loss = initial weight – final weight / final weight × 100

7. **In vitro drug dissolution study**

Dissolution study was carried out using USP type 2 (paddle apparatus) with 300ml of simulated salivary fluid (pH 6.8) as dissolution medium maintained at 37 ± 0.5°C. Medium was stirred at 100 rpm. Samples were withdrawn at every 30 second interval, replacing with the same amount with the fresh medium. Absorbance was determined by UV Spectrophotometer.[2,23]

8. **Stability studies**

The film also subjected to stability studies by storing them for 60 days under environmental condition such as 30±2 °C/65% RH, oven temperature of 40 ± 2 °C /75% RH as per ICH guidelines at time intervals 0, 7, 14, 28, 42 and 60 days. Film were evaluated for change in physical parameters, drug release and drug content.[14]

Market potential

The understanding of the market potential of mouth dissolving films is essential with an industrial point of view to ensure its future growth. As per the market

projection study for 2015-2025, owns a good perspective of growth as an upcoming technology of drug delivery. Ten mouth dissolving films are in the market, and twenty-nine are in the stage of various clinical and preclinical trails out of which six products were launched in 2016. Around to proprietary technologies like Pharm Film, RapidFilm, Bio-FX, etc. are coming up which has 38% market. Thus, it is a potential ground for research and idea of the demand for drug products as mouth dissolving films is expected to be worth US$ 15,984.3 million by the end of 2024. The worldwide market is estimated to exhibit a compound annual growth rate (CAGR) of 9.0% with a significant increase of compound annual growth rate (CAGR) of 18.3% between 2016-2024. North America is having a leading market share of 85.3%.

Targeting of drugs is yet to be covered under this technology. About 54% of products are oral transmucosal films. By sublingual, buccal or oral mucosal route these films can be administered, providing an advantage of rapid onset of action. Some of these products (approx. 38%) depend on MonoSol's Pharm Film innovation or Applied Pharma research/labtec Rapid Film innovation. In count to these two, there are over ten other proprietary oral thin film technologies, some of these are currently being utilized for formulating over-the-counter products. The trending OTC drug products are Gas X and Listerine breath freshener. Some of the new businesses like Cynapsus Therapeutics and FFT Medicals have currently developed and these new upcoming establishments with their oral transmucosal film products are probably going to foster more advancement in the coming couple of years. Of all the showcased products, Suboxone film has obtained acceptance in a short period; other products such as Breakyl, Onsolis and Zuplenz are also progressing in various topographies. Even India is concentrating on film technology due to which within a short span new companies have emerged such as Aavishkar Pvt. Ltd and NU therapeutics in Hyderabad while ZYM laboratories in Nagpur.

The extensive literature survey is mostly based on patents of variousmouth dissolving films from multiple patents bodies across the world such as the United States Patent and Trademark Office (USPTO), World Intellectual Property Right Organization (WIPO), European patent office (EPO) and Indian Patent Office (IPO). The maximum patent filling was found in the United States Patent and Trademark Office (USPTO) of drugs such as sildenafil citrate, dextromethorphan, acetaminophen, buprenorphine and naloxone. India has also established in the market for mouth dissolving films as pharmaceutical companies such as MonoSol Rx, Warner-Lambert and LtsLohmann have filed patents in Indian Patent Office (IPO). The key players in theoral film market are MonoSol Rx, Applied pharma research/labtec, Pfizer, Novartis AG, Wolters Kluwer, Solvay and Allergen.

There are still variousmouth dissolving films under development such as Montelukast which is used for the treatment of asthma and allergy, and Rizatriptan which is used for the treatment of migraine is developed as a film by MonoSol Rx. Moreover, MonoSol Rx is formulating a testosterone film based therapeutic for the treatment of male hypogonadism and the product is present in Phase-I. Also, Midatech, organization expertise is nanotechnology is joining hands with MonoSol Rx to formulate film-based insulin. (Sach Associates, 5th annual European Life Science CEP Forum for partnering and Investing, March 6-7, 2012, Zurich, Switzerland,). Undergraduate biomedical engineering students of Johns Hopkins University have formulated a newmouth dissolving film used as breath revitalizer. Bound with the antibody against Rotavirus the strips can be utilized to give the immunization to infants or newborn children in ruined areas. Thus it can be concluded that there is an exponential increase in research in the field of oral films which will substantially influence the pharmaceutical market in the future.[26]

Table 2: Some patentelmouth dissolving films.[6]

Country	Patent number	Title	Inventors
US	20110305768A1	Quick dissolving oral thin film for targeted delivery of therapeutic agents	Hai-Quan Mao *et al.*
WO	2012103464A2	Oral thin film vaccine preparation	Brian Pulliam
US	5948430	Water-soluble film for oral administration with instant wettability	Zerbe*et al.*
WO	2013085224A1	Bitter taste masked oral thin film formulation of Sildenafil citrate	Dae-Kun Song *et al.*
EP	1680079A2	Rapidly disintegrating films for delivery of pharmaceutical and cosmetic agents	Scott D Bamhart*et al.*
EP	2509631A4	pH-sensitive compounds in taste masking within oral thin films strips	A Mark Schobel*et al.*
WO	2012053006A2	Improved oral fast dissolving films comprising a combination of polymers and method of preparation thereof	Rajesh Jain *et al.*
US	6596298B2	Fast dissolving orally consumable films	Sau-Hung Spence Leung *et al.*

WO	2014183054A1	The thin film with a high load of active ingredient	Eric Allen *et al.*
US	7579019B2	Pharmaceutical carrier device suitable for the delivery of pharmaceutical compounds to the mucosal surface	Tapolsky*et al.*
US	6159498	Bioerodable film for delivery of pharmaceutical compounds of the mucosal surface	Tapolsky*et al.*
US	6824829B2	Process for manufacturing thin film strip	Berry *et al.*
US	7132113B2	Flavored film	Zerbe*et al.*
US	7182964B2	Dissolving thin film xanthone supplement	Kupper*et al.*
US	7241411B2	Thin film strip	Berry *et al.*
US	7267718B2	Pullulan film composition	Scott *et al.*
US	7347985B2	Breath freshening and oral cleansing product with a magnolia bark extract	Maxwell *et al.*
US	1648712B2	A fast dissolving orally consumable film containing taste masking agent	Bess *et al.*

CONCLUSION

From the present review it can be concluded that MDFs offers many advantages over more traditional delivery methods like tablets, capsules and syrups in terms of production, handling, transportation, administration, mechanism of action and stability. The method of preparation was found to be simple, requiring minimum excipients that making the product more cost effective. Presently MDFs are widely available for hypertension, acidity, allergy, vomiting etc. which gives enhanced bioavailability and fast onset of action for patient convenience and compliance, have glowing futuristic opportunities.

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